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PATENT APPLICATION  
Mo-6466  
LeA 34,706

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICATION OF )  
ALEXANDER KLAUSENER ET AL ) GROUP NO.: 1626  
SERIAL NUMBER: 09/899,421 ) EXAMINER: G.M. SHAMEEM  
FILED: JULY 5, 2001 )  
TITLE: PROCESS FOR PREPARING 2-ALKYL- )  
3-ARYL- AND -HETEROARYLOXA- )  
ZIRIDINES, AND NOVEL 2-ALKYL- )  
3-ARYLOXAZIRIDINES )

LETTER

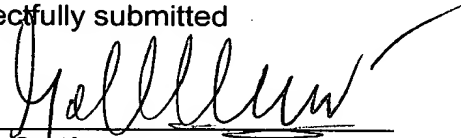
Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 2231-1450

Sir:

Enclosed herewith are three copies of an Appeal Brief in the matter of the subject Appeal. Please charge the fee for filing the Brief, \$330.00, to our Deposit Account Number **50-2527**.

Respectfully submitted

By

  
Godfried R. Akorli  
Attorney for Appellants  
Reg. No. 28,779

BAYER CHEMICALS CORPORATION  
100 Bayer Road  
Pittsburgh, PA 15205-9741  
Phone: (412) 777-3061  
FACSIMILE PHONE NUMBER:  
(412) 777-3902

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Commissioner for Patents, Alexandria, VA 22313-1450, on November 25, 2003  
Date

Godfried R. Akorli Reg. No. 28,779  
Name of applicant, Assignee or Registered Representative

  
Signature

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APPEAL BRIEF

Commissioner for Patents  
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Date  
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#### I. REAL PARTY IN INTEREST

The real party in interest for the present appeal is the assignee Bayer AG.

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Appellants are unaware of other appeals or interferences that will directly affect or be directly affected by or having a bearing on the present appeal.

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The above-referenced application was filed with Claims 1-11, of which Claims 10 and 11 were withdrawn subject to a restriction requirement. Claims 1- 9 which remain in the application are the subject of this appeal.

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#### SUMMARY OF THE INVENTION

This invention provides a process for preparing 2-alkyl-3-aryl- and heteroaryloxaziridines comprising oxidizing corresponding N-alkyl-aryl- or -heteroarylaldimines with an aromatic percarboxylic acid or a salt thereof in the presence of water, a water-soluble base, and a water-miscible solvent, at temperatures below 30°C. See page 3, lines 5-9 of the captioned application

It is of note that, while the preparation and handling of percarboxylic acids is safer if water is present during their preparation and use, for example during oxidations, the presence of acids and water, imines generally tend to hydrolyze. This is the reason why the presence of water has been substantially excluded in the known imine oxidations.

Furthermore, the presence of acid and water in the reaction medium used for Mo-6466

preparing oxaziridines promotes hydrolytic cleavage of the oxaziridines formed into the corresponding aldehyde and the corresponding N-substituted hydroxylamine. The latter for its part is readily oxidized by the percarboxylic acid present to give the corresponding nitroso compound. Nitroso compounds are known to be substances which are highly carcinogenic. Accordingly, they have to be excluded in the preparation of intermediates for pharmaceutically active compounds. See page 2, lines 9-21 of the captioned application

Heretofore, none of the known methods for preparing aryloxaziridines by oxidizing arylamines with percarboxylic acids are satisfactory for industrial-scale processes. Accordingly, there is still a need for a simple, economical and low-risk process for preparing 2-alkyl-3-aryl- and heteroaryloxaziridines. See page 2, lines 29 through page 3, line 3 of the captioned application.

## VI. ISSUES

### Issue 1

Whether the Examiner erred in rejecting Claim 1-9 under 35 USC 103 as being unpatentable over Kimm et al (US 2784182) in view of Shirmann, et al (US 3819653) where the record does not provide a basis for the proposed modification of adding water to water-miscible solvents in the claimed process.

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Claims are placed in the same grouping.

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Appellants have traversed the rejection for lack of prima facie obviousness in that the record does not provide a basis for the Examiner's proposed modification, with a reasonable expectation of success. More specifically, the record does not provide a basis proposed modification of adding water to water-miscible solvents in the claimed process, in face of the art-known problems associated with such addition.

Seemingly, the Examiner in the final office action seems to be arguing that the burden is met by the overruled holding which has been characterized as the "Winslow Tableau" (In re Winslow, 151 USPQ 48 CCPA 1966) wherein the skilled artisan is presumed to be aware of the all pertinent art.

Based on the premise of the Winslow Tableau, the Examiner argues against Appellants' arguments relating lack of prima facie obviousness as follows:

"This assessment is speculation on applicant's behalf because one of ordinary skill in the art deemed to be aware of all the pertinent art in the field."

Appellants submit that the Examiner characterization of Appellants' argument of lack of prima facie obviousness, and the apparent requirement of proof in support of such argument is against the weight of authority in the patent laws. It is well established that the Examiner must point to factual basis in the references or the general knowledge in the art. It is insufficient to state that the one skilled in the art would be aware of such basis, without any support therefor.

Seemingly based on the premise of the Winslow Tableau, the Examiner concludes without factual support that the claims fall within the generic process of the prior art, that the prior art teaches "several combinations" which would lead to the claims, and that the prior art can be optimized to the claims.

These unsupported conclusions are discussed and refuted more fully hereunder. At page 3, last paragraph through page 4, line 2 of the Office Action, the Examiner argues without factual support that:

"The prior art teach generic process of preparing oxaziridines using analogous reagents such as aldehydes (column 2, line 67 of US '182), mono-peroxy phthalic acid (column 3, line 38 of US '182), water-miscible solvent e.g. chlorobenzene (col. 3, line 69 of US '182), at an overlapping temperature range. The differences between the instant claims and the prior art are so negligible, that one of ordinary skill in the chemical art would expect slight variations to be within the expected purview of 35 U.S.C. 103(a)." (Delineation is Appellants for emphasis).

Appellants submit that statements such as the reagents are analogous and that the differences are negligible are mere conclusions, which are not based on facts.

Appellants hasten to note that the Examiner has not ascertained the negligible differences between the prior art and the claims. Therefore, Appellants requested that the Examiner ascertain the negligible differences between the prior art and the claims. As of the filing of this Appeal Brief, the Examiner has not communicated the nature of the negligible difference to Appellants.

Appellants, for their part, have stated that the claims differ from the prior art in at least one respect in failing to teach or suggest the addition of water to water-miscible solvents. Appellants have shown why the skilled artisan would not have added water to water-miscible solvents, in the preparation of the referenced compounds, let alone the claimed compounds. In this regard, Appellants direct the Board's attention to page 2, lines 9-21, which states that:

"In general, the preparation and handling of percarboxylic acids is safer if water is present during their preparation and use, for example during oxidations. However, in the presence of acids and

water, imines generally tend to hydrolyze. This is the reason why the presence of water has been substantially excluded in the known imine oxidations.

Furthermore, the presence of acid and water in the reaction medium used for preparing oxaziridines promotes hydrolytic cleavage of the oxaziridines formed into the corresponding aldehyde and the corresponding N-substituted hydroxylamine. The latter for its part is readily oxidized by the percarboxylic acid present to give the corresponding nitroso compound. Nitroso compounds are known to be substances which are highly carcinogenic. Accordingly, they have to be excluded in the preparation of intermediates for pharmaceutically active compounds."

Appellants' position remains undisputed by facts of record.

Therefore, Appellants requested that should the Examiner continue to rely on general knowledge, the Examiner should provide data supporting the assertion that such an addition is within the general knowledge of the skilled artisan, In re Lee, 61 USPQ 1430 61 USPQ2d 1430 (CAFC 2000). As of the date of filing of this Appeal Brief not such data has been provided.

At page 4, lines 2-6 of the Office Action, the Examiner argues for the combination of the references without factual support for making the proposed combinations.

Specifically the Examiner argues that:

"The disclosure of Krimm et al and further in view of Schirmann et al or Bulachkova et al teach several combinations that would easily place Appellants' invention in possession of the public at the time of Appellants' invention was filed. The motivation to make the claimed process derives from the expectation that the use of analogous reagents under specific set of reaction conditions would have made similar products." (Delineation is Appellants)

At page 4, lines 6-10, the Examiner reiterated his arguments about optimization without any factual support by stating that:

“The determination of optimum reaction conditions is routine experimentation and to one skilled in the art. Changes in temperature, concentration of reactants, or both are not patentable modification in the absence of unexpected results, which is different in kind and not degree (In re Boesch 205 USPQ, 215 CCPA 1980)”

Finally, at page 4, lines 10-13, the Examiner states without factual support that there are exemplary teachings of the process in the art. Specifically, the Examiner states that:

“Since there is an exemplary teaching of a process to obtain the claimed compounds in the prior art, one would have reasonable expectation that such modification and optimization of reaction conditions would give compounds with similar rate of recovery.”

The Examiner has not identified an example of the claimed process in the cited references.

From the foregoing, it is quite clear that the Examiner has not advanced factual support for his conclusion of obviousness. Hence, there remains the issue of whether the Examiner has indeed established a prima facie case of obviousness based on the cited references.

It is well settled in the law that to establish prima facie case obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

It is also well settled in the law that the teaching to make the claimed combination and the reasonable expectation of success must both be found the prior art and not based on applicant's disclosure, In re Vaeck 20 USPQ2d 1438 (Fed. Cir. 1991).

The initial burden is on the Examiner to provide some suggestion of desirability of Mo-6466



doing what the inventor has done. The references must explicitly or implicitly suggest the claimed invention, or the Examiner must present a convincing line of reasoning as to why the skilled artisan would have found the claimed invention to be obvious.

In this case, the record does not point to how the skilled artisan having the references before him would have modified the prior art to the claims. The mere fact that the references can be combined or modified does not render the proposed combination obvious unless the prior art suggests the desirability of making the combination as discussed above. The mere fact that the references fall within the broad class of the prior art does not render the claims obvious, absent some basis in the art for making the proposed modification. Other than the unsupported assertion of general knowledge, the Examiner has not pointed to evidence or practical reason supporting his proposed modification.

Where the Examiner has not established a prima facie case, Appellants do not need to submit any evidence of nonobviousness in rebuttal.

Nonetheless, Appellants in their responses to the office actions have provided ample reasons supporting their assertion that the Examiner has failed to make a prima facie case of obviousness. Appellants' arguments are stated hereunder.

The Examiner's proposed combination of references does not lead to the claims encompassing a mixture of water and a water-miscible solvent. For, adding more water to the process of Krimm et al would have led to an unsatisfactory combination of water and water-miscible organic solvent. Where the proposed modification would be unsatisfactory, it cannot be said to render the claims obvious, In re Gordon 221 USPQ 1125 (Fed Cir. 1984). For, it is well known that the presence of water is detrimental for the reaction of imines with per-compounds. In the presence of acids and water, the imines used as starting materials tend to hydrolyze, thereby lowering the yield achieved. Additionally, the presence of water and acid results in a hydrolytic cleavage of the oxaziridines formed into corresponding aldehyde and the corresponding NO-substituted hydroxylamine. The latter is easily oxidized to give an

undesired nitroso-compound as by-product. These side-reactions additionally lower the yield (see the captioned application, at page 2, lines 12-15 and lines 17-23). These undesired consequences relating to the presence of water are reflected by the poor yields achieved in the Krimm process.

Appellants further traverse the rejection based on the assertion that the addition of water constitutes optimization. It is well established that a particular parameter must first be recognized as result-effective, i.e., a variable which achieves a recognized result before the determination of the optimum or workable range of said variable, In re Antonie 195 USPQ 6 (CCPA 1997). In this case, the record does not show that the addition of water was recognized as a result-effective variable. Therefore, a basis for arguing optimization has not been established. In view of the foregoing, Appellants submit that Krimm in view of Schirrmann does not support a case of prima facie obviousness.

Quite instructive is the teaching of Bulachkova, which relates to preparation of oxaziridines by reacting imines with perbenzoic acid, wherein the reaction is carried out as a phase transfer epoxidization. This means that the reaction system comprises water and a non-water miscible organic solvent, as well as a phase-transfer catalyst. The Examiner has not stated how the combination of water and non-water miscible organic solvent teaches or suggests the claims. To be sure, two-phase systems without a phase transfer-catalyst are known in the preparation of oxaziridines, as acknowledged by the citation of WO-A-00/02848 at page 2, line 25ff of the captioned application. However process employing these systems are disadvantaged, if up scaling of the reaction is intended.

The record is devoid of a basis in Schirrmann for modifying Bulachkova in order to overcome its disadvantages such as those associated with scaling up the reaction. Therefore Bulachkova, in view of Schirrmann, fails to support a case for prima facie obviousness.

Finally, Appellants submit that the Examiner ignored or dismissed as optimization Mo-6466

the marked improvements that attend the process. The combination of water with water-miscible solvent results in the observed high yields of the desired oxaziridines. Additionally the addition of a base during the reaction – and not afterwards - results in further improvement of the yield, by reducing the acidic side reactions described above. Also, the presence of water according to the present invention makes the handling of the percarboxylic acid safer.

The Examiner has failed to show that combination of water with water-miscible solvents would results in improvement in yield of oxaziridines. The Examiner has failed to show that the order of addition of a based would result in improvement in yield.

In view of the foregoing which rebuts the reasons for the proposed modification, it is untenable to suggest that the proposed modifications would have led to the claims. It is untenable to suggest the addition of water to Krimm et al process where the proposed modification as shown above would be unsatisfactory. It is untenable to suggest that Shirmann's teaching of preparing oxaziridines by reacting imine with hydrogen peroxide in the presence of nitrile suggest the addition of water. Such a suggestion would be impermissibly based on picking and choosing the ingredients of the prior art in light of Appellants' disclosure. Finally it would be untenable to

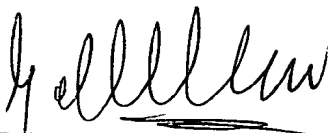
suggest that Bulachkova et al's teaching of a reaction system comprising water and a non-water miscible organic solvent, as well as a phase-transfer catalyst would have suggested the use of water in combination with water-miscible solvent.

With respect to this identified difference, it is clear that the Examiner has not established factual support for the conclusion of obviousness. Therefore, Applicant prays for the withdrawal of the rejection and allowance of the claims.

In the alternative, and for the purpose of appeal, Appellants request an explicit statement of the differences between the prior art and the claims, and data in support of the assertion that the differences would have been within the general

knowledge of the skilled artisan.

Respectfully submitted,

By 

Godfried R. Akorli  
Attorney for Appellants  
Reg. No. 28,779

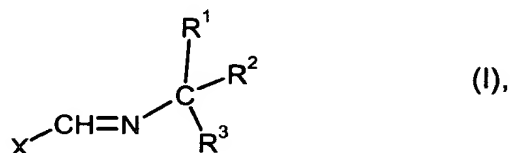
Bayer Chemicals Corporation  
100 Bayer Road  
Pittsburgh, Pennsylvania 15205-9741  
(412) 777-3061  
FACSIMILE PHONE NUMBER:  
(412) 777- 2612

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## APPENDIX: CLAIMS ON APPEAL

1. A process for preparing a 2-alkyl-aryl- or -heteroaryloxaziridine comprising oxidizing a corresponding N-alkyl-aryl- or -heteroarylaldehyde with an aromatic percarboxylic acid or a salt thereof in the presence of water, a water-soluble base, and a water-miscible solvent, at temperatures below 30°C.

2. A process according to Claim 1 wherein an N-alkyl-aryl- or -heteroarylaldehyde of the formula (I)



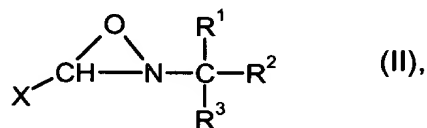
wherein

R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> independently of one another each represent hydrogen, straight-chain or branched C<sub>1</sub>-C<sub>20</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, straight-chain or branched C<sub>2</sub>-C<sub>10</sub>-alkenyl, or C<sub>6</sub>-C<sub>10</sub>-aryl, or the entire C(R<sup>1</sup>)(R<sup>2</sup>)(R<sup>3</sup>) group represents a C<sub>3</sub>-C<sub>8</sub>-cycloalkyl radical, and

X represents C<sub>6</sub>-C<sub>12</sub>-aryl or heteroaryl having 4 or 5 C atoms and 1 or 2 identical or different heteroatoms selected from the group consisting of N, O, and S,

wherein all alkyl, cycloalkyl, alkenyl, aryl, and heteroaryl radicals may optionally be mono- or polysubstituted,

is oxidized to form the corresponding 2-alkyl-3-aryl- or -heteroaryloxaziridines of the formula (II)



in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and X are as defined for formula (I).

3. A process according to Claim 2 wherein one or more alkyl radicals are mono- or polysubstituted by saturated C<sub>3</sub>-C<sub>12</sub>-cycloalkyl, C<sub>6</sub>-C<sub>10</sub>-aryl, C<sub>2</sub>-C<sub>8</sub>-alkenyl, fluorine, chlorine, bromine, iodine, hydroxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>6</sub>-C<sub>10</sub>-aryloxy,

carboxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, nitro, amido, nitrile, sulfonyl, or phosphate and wherein one or more cycloalkyl, alkenyl, aryl, and heteroaryl radicals are mono- or polysubstituted by C<sub>1</sub>-C<sub>6</sub>-alkyl, fluorine, chlorine, bromine, hydroxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, carboxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, nitro, sulfonyl, or nitrile.

4. A process according to Claim 2 wherein in formulas (I) and (II), R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> independently of one another each represent hydrogen, straight-chain or branched C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, straight-chain or branched C<sub>3</sub>-C<sub>6</sub>-alkenyl, or phenyl or the entire C(R<sup>1</sup>)(R<sup>2</sup>)(R<sup>3</sup>) group represents C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, wherein the radicals are not substituted any further, and X represents phenyl, naphthyl, or furyl, wherein the phenyl and naphthyl radicals may optionally be substituted by one or two identical or different radicals selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, fluorine, chlorine, bromine, hydroxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, nitro, sulfonyl, and nitrile.

5. A process according to Claim 1 wherein the percarboxylic acid or the salt thereof is m-chloroperbenzoic acid or monoperoxyphthalic acid or an alkali metal or magnesium salt thereof.

6. A process according to Claim 1 wherein the water-soluble base is an alkali metal or alkaline earth metal oxide, hydroxide, carbonate, bicarbonate, hydrogen phosphate, or dihydrogen phosphate.

7. A process according to Claim 1 wherein the water-miscible solvent is a mono- or polyhydric alcohol having up to 6 C atoms.

8. A process according to Claim 2 comprising

- (1) initially preparing a mixture comprising 5 to 80% by weight of the aldimine of the formula (I) in the water-miscible solvent,
- (2) reacting the mixture with the aqueous solution comprising 15 to 30% by weight of a base,
- (3) adding a 1 to 20% by weight strength solution of an aromatic percarboxylic acid or a salt thereof to the resulting mixture at such a rate that the reaction temperature does not exceed 30°C,
- (4) stirring the resulting mixture at from 5 to 30°C until the reaction has ended, and

- (5) working up the reaction mixture by phase separation or extraction.
9. A process according to Claim 2 wherein, based on the aldimine of the formula (I), from 0.09 to 2 equivalents of base and from 0.9 to 1.2 equivalents of active oxygen in the form of an aromatic percarboxylic acid or salt thereof are used.
10. 2-Isopropyl-3-(4-methoxyphenyl)oxaziridine.
11. 2-n-Propyl-3-(4-methoxyphenyl)oxaziridine.



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These unsupported conclusions are discussed and refuted more fully hereunder. At page 3, last paragraph through page 4, line 2 of the Office Action, the Examiner argues without factual support that:

"The prior art teach generic process of preparing oxaziridines using analogous reagents such as aldehydes (column 2, line 67 of US '182), mono-peroxy phthalic acid (column 3, line 38 of US '182), water-miscible solvent e.g. chlorobenzene (col. 3, line 69 of US '182), at an overlapping temperature range. The differences between the instant claims and the prior art are so negligible, that one of ordinary skill in the chemical art would expect slight variations to be within the expected purview of 35 U.S.C. 103(a)." (Delineation is Appellants for emphasis).

Appellants submit that statements such as the reagents are analogous and that the differences are negligible are mere conclusions, which are not based on facts. Appellants hasten to note that the Examiner has not ascertained the negligible differences between the prior art and the claims. Therefore, Appellants requested that the Examiner ascertain the negligible differences between the prior art and the claims. As of the filing of this Appeal Brief, the Examiner has not communicated the nature of the negligible difference to Appellants.

Appellants, for their part, have stated that the claims differ from the prior art in at least one respect in failing to teach or suggest the addition of water to water-miscible solvents. Appellants have shown why the skilled artisan would not have added water to water-miscible solvents, in the preparation of the referenced compounds, let alone the claimed compounds. In this regard, Appellants direct the Board's attention to page 2, lines 9-21, which states that:

"In general, the preparation and handling of percarboxylic acids is safer if water is present during their preparation and use, for example during oxidations. However, in the presence of acids and

water, imines generally tend to hydrolyze. This is the reason why the presence of water has been substantially excluded in the known imine oxidations.

Furthermore, the presence of acid and water in the reaction medium used for preparing oxaziridines promotes hydrolytic cleavage of the oxaziridines formed into the corresponding aldehyde and the corresponding N-substituted hydroxylamine. The latter for its part is readily oxidized by the percarboxylic acid present to give the corresponding nitroso compound. Nitroso compounds are known to be substances which are highly carcinogenic. Accordingly, they have to be excluded in the preparation of intermediates for pharmaceutically active compounds."

Appellants' position remains undisputed by facts of record.

Therefore, Appellants requested that should the Examiner continue to rely on general knowledge, the Examiner should provide data supporting the assertion that such an addition is within the general knowledge of the skilled artisan, In re Lee, 61 USPQ 1430 61 USPQ2d 1430 (CAFC 2000). As of the date of filing of this Appeal Brief not such data has been provided.

At page 4, lines 2-6 of the Office Action, the Examiner argues for the combination of the references without factual support for making the proposed combinations.

Specifically the Examiner argues that:

"The disclosure of Krimm et al and further in view of Schirmann et al or Bulachkova et al teach several combinations that would easily place Appellants' invention in possession of the public at the time of Appellants' invention was filed. The motivation to make the claimed process derives from the expectation that the use of analogous reagents under specific set of reaction conditions would have made similar products." (Delineation is Appellants)

At page 4, lines 6-10, the Examiner reiterated his arguments about optimization without any factual support by stating that:

"The determination of optimum reaction conditions is routine experimentation and to one skilled in the art. Changes in temperature, concentration of reactants, or both are not patentable modification in the absence of unexpected results, which is different in kind and not degree (In re Boesch 205 USPQ, 215 CCPA 1980)"

Finally, at page 4, lines 10-13, the Examiner states without factual support that there are exemplary teachings of the process in the art. Specifically, the Examiner states that:

"Since there is an exemplary teaching of a process to obtain the claimed compounds in the prior art, one would have reasonable expectation that such modification and optimization of reaction conditions would give compounds with similar rate of recovery."

The Examiner has not identified an example of the claimed process in the cited references.

From the foregoing, it is quite clear that the Examiner has not advanced factual support for his conclusion of obviousness. Hence, there remains the issue of whether the Examiner has indeed established a prima facie case of obviousness based on the cited references.

It is well settled in the law that to establish prima facie case obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

It is also well settled in the law that the teaching to make the claimed combination and the reasonable expectation of success must both be found the prior art and not based on applicant's disclosure, In re Vaeck 20 USPQ2d 1438 (Fed. Cir. 1991).

The initial burden is on the Examiner to provide some suggestion of desirability of

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doing what the inventor has done. The references must explicitly or implicitly suggest the claimed invention, or the Examiner must present a convincing line of reasoning as to why the skilled artisan would have found the claimed invention to be obvious.

In this case, the record does not point to how the skilled artisan having the references before him would have modified the prior art to the claims. The mere fact that the references can be combined or modified does not render the proposed combination obvious unless the prior art suggests the desirability of making the combination as discussed above. The mere fact that the references fall within the broad class of the prior art does not render the claims obvious, absent some basis in the art for making the proposed modification. Other than the unsupported assertion of general knowledge, the Examiner has not pointed to evidence or practical reason supporting his proposed modification.

Where the Examiner has not established a prima facie case, Appellants do not need to submit any evidence of nonobviousness in rebuttal.

Nonetheless, Appellants in their responses to the office actions have provided ample reasons supporting their assertion that the Examiner has failed to make a prima facie case of obviousness. Appellants' arguments are stated hereunder.

The Examiner's proposed combination of references does not lead to the claims encompassing a mixture of water and a water-miscible solvent. For, adding more water to the process of Krimm et al would have led to an unsatisfactory combination of water and water-miscible organic solvent. Where the proposed modification would be unsatisfactory, it cannot be said to render the claims obvious, In re Gordon 221 USPQ 1125 (Fed Cir. 1984). For, it is well known that the presence of water is detrimental for the reaction of imines with per-compounds. In the presence of acids and water, the imines used as starting materials tend to hydrolyze, thereby lowering the yield achieved. Additionally, the presence of water and acid results in a hydrolytic cleavage of the oxaziridines formed into corresponding aldehyde and the corresponding NO-substituted hydroxylamine. The latter is easily oxidized to give an

undesired nitroso-compound as by-product. These side-reactions additionally lower the yield (see the captioned application, at page 2, lines 12-15 and lines 17-23). These undesired consequences relating to the presence of water are reflected by the poor yields achieved in the Krimm process.

Appellants further traverse the rejection based on the assertion that the addition of water constitutes optimization. It is well established that a particular parameter must first be recognized as result-effective, i.e., a variable which achieves a recognized result before the determination of the optimum or workable range of said variable, In re Antonie 195 USPQ 6 (CCPA 1997). In this case, the record does not show that the addition of water was recognized as a result-effective variable. Therefore, a basis for arguing optimization has not been established. In view of the foregoing, Appellants submit that Krimm in view of Schirmann does not support a case of prima facie obviousness.

Quite instructive is the teaching of Bulachkova, which relates to preparation of oxaziridines by reacting imines with perbenzoic acid, wherein the reaction is carried out as a phase transfer epoxidization. This means that the reaction system comprises water and a non-water miscible organic solvent, as well as a phase-transfer catalyst. The Examiner has not stated how the combination of water and non-water miscible organic solvent teaches or suggests the claims.

To be sure, two-phase systems without a phase transfer-catalyst are known in the preparation of oxaziridines, as acknowledged by the citation of WO-A-00/02848 at page 2, line 25ff of the captioned application. However process employing these systems are disadvantaged, if up scaling of the reaction is intended.

The record is devoid of a basis in Schirmann for modifying Bulachkova in order to overcome its disadvantages such as those associated with scaling up the reaction. Therefore Bulachkova, in view of Schirmann, fails to support a case for prima facie obviousness.

Finally, Appellants submit that the Examiner ignored or dismissed as optimization



the marked improvements that attend the process. The combination of water with water-miscible solvent results in the observed high yields of the desired oxaziridines. Additionally the addition of a base during the reaction – and not afterwards - results in further improvement of the yield, by reducing the acidic side reactions described above. Also, the presence of water according to the present invention makes the handling of the percarboxylic acid safer.

The Examiner has failed to show that combination of water with water-miscible solvents would results in improvement in yield of oxaziridines. The Examiner has failed to show that the order of addition of a based would result in improvement in yield.

In view of the foregoing which rebuts the reasons for the proposed modification, it is untenable to suggest that the proposed modifications would have led to the claims. It is untenable to suggest the addition of water to Krimm et al process where the proposed modification as shown above would be unsatisfactory. It is untenable to suggest that Shirmann's teaching of preparing oxaziridines by reacting imine with hydrogen peroxide in the presence of nitrile suggest the addition of water. Such a suggestion would be impermissibly based on picking and choosing the ingredients of the prior art in light of Appellants' disclosure. Finally it would be untenable to

suggest that Bulachkova et al's teaching of a reaction system comprising water and a non-water miscible organic solvent, as well as a phase-transfer catalyst would have suggested the use of water in combination with water-miscible solvent.

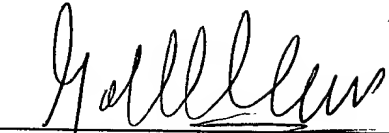
With respect to this identified difference, it is clear that the Examiner has not established factual support for the conclusion of obviousness. Therefore, Applicant prays for the withdrawal of the rejection and allowance of the claims.

In the alternative, and for the purpose of appeal, Appellants request an explicit statement of the differences between the prior art and the claims, and data in support of the assertion that the differences would have been within the general

knowledge of the skilled artisan.

Respectfully submitted,

By



Godfried R. Akorli  
Attorney for Appellants  
Reg. No. 28,779

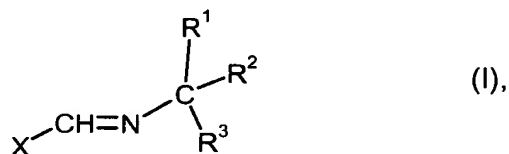
Bayer Chemicals Corporation  
100 Bayer Road  
Pittsburgh, Pennsylvania 15205-9741  
(412) 777-3061  
FACSIMILE PHONE NUMBER:  
(412) 777- 2612

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## APPENDIX: CLAIMS ON APPEAL

1. A process for preparing a 2-alkyl-aryl- or -heteroaryloxaziridine comprising oxidizing a corresponding N-alkyl-aryl- or -heteroarylaldimine with an aromatic percarboxylic acid or a salt thereof in the presence of water, a water-soluble base, and a water-miscible solvent, at temperatures below 30°C.

2. A process according to Claim 1 wherein an N-alkyl-aryl- or -heteroarylaldimine of the formula (I)



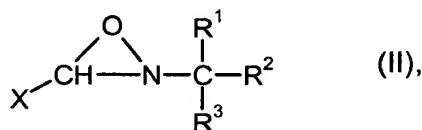
wherein

R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> independently of one another each represent hydrogen, straight-chain or branched C<sub>1</sub>-C<sub>20</sub>-alkyl, C<sub>3</sub>-C<sub>8</sub>-cycloalkyl, straight-chain or branched C<sub>2</sub>-C<sub>10</sub>-alkenyl, or C<sub>6</sub>-C<sub>10</sub>-aryl, or the entire C(R<sup>1</sup>)(R<sup>2</sup>)(R<sup>3</sup>) group represents a C<sub>3</sub>-C<sub>8</sub>-cycloalkyl radical, and

X represents C<sub>6</sub>-C<sub>12</sub>-aryl or heteroaryl having 4 or 5 C atoms and 1 or 2 identical or different heteroatoms selected from the group consisting of N, O, and S,

wherein all alkyl, cycloalkyl, alkenyl, aryl, and heteroaryl radicals may optionally be mono- or polysubstituted,

is oxidized to form the corresponding 2-alkyl-3-aryl- or -heteroaryloxaziridines of the formula (II)



in which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and X are as defined for formula (I).

3. A process according to Claim 2 wherein one or more alkyl radicals are mono- or polysubstituted by saturated C<sub>3</sub>-C<sub>12</sub>-cycloalkyl, C<sub>6</sub>-C<sub>10</sub>-aryl, C<sub>2</sub>-C<sub>8</sub>-alkenyl, fluorine, chlorine, bromine, iodine, hydroxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, C<sub>6</sub>-C<sub>10</sub>-aryloxy,

carboxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, nitro, amido, nitrile, sulfonyl, or phosphate and wherein one or more cycloalkyl, alkenyl, aryl, and heteroaryl radicals are mono- or polysubstituted by C<sub>1</sub>-C<sub>6</sub>-alkyl, fluorine, chlorine, bromine, hydroxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxy, carboxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, nitro, sulfonyl, or nitrile.

4. A process according to Claim 2 wherein in formulas (I) and (II), R<sup>1</sup>, R<sup>2</sup>, and R<sup>3</sup> independently of one another each represent hydrogen, straight-chain or branched C<sub>1</sub>-C<sub>10</sub>-alkyl, C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, straight-chain or branched C<sub>3</sub>-C<sub>6</sub>-alkenyl, or phenyl or the entire C(R<sup>1</sup>)(R<sup>2</sup>)(R<sup>3</sup>) group represents C<sub>3</sub>-C<sub>6</sub>-cycloalkyl, wherein the radicals are not substituted any further, and X represents phenyl, naphthyl, or furyl, wherein the phenyl and naphthyl radicals may optionally be substituted by one or two identical or different radicals selected from the group consisting of C<sub>1</sub>-C<sub>6</sub>-alkyl, fluorine, chlorine, bromine, hydroxyl, C<sub>1</sub>-C<sub>6</sub>-alkoxycarbonyl, nitro, sulfonyl, and nitrile.

5. A process according to Claim 1 wherein the percarboxylic acid or the salt thereof is m-chloroperbenzoic acid or monoperoxyphthalic acid or an alkali metal or magnesium salt thereof.

6. A process according to Claim 1 wherein the water-soluble base is an alkali metal or alkaline earth metal oxide, hydroxide, carbonate, bicarbonate, hydrogen phosphate, or dihydrogen phosphate.

7. A process according to Claim 1 wherein the water-miscible solvent is a mono- or polyhydric alcohol having up to 6 C atoms.

8. A process according to Claim 2 comprising

- (1) initially preparing a mixture comprising 5 to 80% by weight of the aldimine of the formula (I) in the water-miscible solvent,
- (2) reacting the mixture with the aqueous solution comprising 15 to 30% by weight of a base,
- (3) adding a 1 to 20% by weight strength solution of an aromatic percarboxylic acid or a salt thereof to the resulting mixture at such a rate that the reaction temperature does not exceed 30°C,
- (4) stirring the resulting mixture at from 5 to 30°C until the reaction has ended, and

- (5) working up the reaction mixture by phase separation or extraction.
9. A process according to Claim 2 wherein, based on the aldimine of the formula (I), from 0.09 to 2 equivalents of base and from 0.9 to 1.2 equivalents of active oxygen in the form of an aromatic percarboxylic acid or salt thereof are used.
10. 2-Isopropyl-3-(4-methoxyphenyl)oxaziridine.
11. 2-n-Propyl-3-(4-methoxyphenyl)oxaziridine.